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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BIOGEN MA INC,
Patent Owner.

Case IPR2018-01403
Patent No. 8,399,514 B2

Before SHERIDAN K. SNEDDEN, JENNIFER MEYER CHAGNON, and JAMIE T. WISZ, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Mylan Pharmaceuticals Inc. ("Petitioner") bears the burden of proving unpatentability of the challenged claims, and that burden of persuasion never shifts to Biogen MA Inc. ("Patent Owner"). *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). The evidentiary standard is a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

For the reasons that follow, we determine that Petitioner has not shown, by a preponderance of the evidence, that challenged claims 1–20 of U.S. Patent No. 8,399,514 B2 (Ex. 1001, "the '514 patent") are unpatentable.

A. Procedural History

Petitioner filed a Petition requesting an *inter partes* review of claims 1–20 of the '514 patent. Paper 2 ("Pet."). Patent Owner filed a Preliminary Response. Paper 7. With prior authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9) to address the Federal Circuit's decision in *FWP IP APS v. Biogen MA Inc.*, 749 F. App'x 969, 972 (Fed. Cir. 2018). Patent Owner filed a Sur-Reply. Paper 10.

Upon consideration of the Petition, Preliminary Response, and the parties' additional briefing, we instituted an *inter partes* review of claims 1–20 of the '514 patent on each ground of unpatentability set forth in the Petition, which are as follows:

Ground	Claims	Basis[1]	References
1	1–20	§ 103(a)	Biogen Press Release[2] and Schimrigk 2004[3]
2	1–20	§ 103(a)	Kappos 2006[4] and Schimrigk 2004
3	1–20	§ 103(a)	Kappos 2006 and WO '342[5]
4	1–20	§ 103(a)	Kappos 2006, Clinical Trials[6], Joshi '999[7], and ICH Guideline[8]

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103. Because the '514 patent was filed before March 16, 2013 (the effective date of the relevant amendment), the pre-AIA version of § 103 applies.

[2] Ex. 1005, Biogen News Release, *Phase II Study of Oral Compound BG-12 Meets Primary Endpoint in Multiple Sclerosis* (Jan. 9, 2006) ("Biogen Press Release").

[3] Ex. 1006, S. Schimrigk et al., *A Prospective, Open-Label, Phase II Study of Oral Fumarate Therapy for the Treatment of Relapsing-Remitting Multiple Sclerosis*, 10 (Suppl. 2) MULTIPLE SCLEROSIS CLIN. & LAB. RES. S258, Abstract P642 (2004) ("Schimrigk 2004").

[4] Ex. 1007, L. Kappos et al., *Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study*, 253 (Suppl. 2) J. NEUROL. II27, O108 (2006) ("Kappos 2006").

[5] Ex. 1008, International Publication No. WO 2006/0037342 A2 (published Apr. 13, 2006) ("WO '342").

[6] Ex. 1010, NCT00168701, CLINICALTRIALS.GOV, https://clinicaltrials.gov/archive/NCT00168701/2005_09_14 ("Clinical Trials").

[7] Ex. 1009, R. K. Joshi et al., U.S. Patent No. 7,320,999, issued Jan. 22, 2008 ("Joshi '999").

[8] Ex. 1011, ICH Harmonised Tripartite Guideline - *Dose-Response Information to Support Drug Registration E4* (Mar. 10, 1994) ("ICH Guideline").

Paper 12.

Subsequently, Patent Owner filed a Patent Owner Response (Paper 38; "PO Resp."), Petitioner filed a Reply (Paper 68; "Reply"), and Patent Owner filed a Sur-Reply (Paper 79; "Sur-Reply").

Petitioner relies upon the Declarations of Dr. John R. Corboy (Ex. 1002), Dr. Leslie Z. Benet (Ex. 1003), and Dr. Ian McKeague (Ex. 1004) to support its contentions. On Reply, Petitioner relies on the Declarations of Dr. Benjamin M. Greenberg (Ex. 1121).[9]

Patent Owner relies upon the Declaration of Dr. Richard C. Brundage (Ex. 2057), Dr. Martin Duddy (Ex. 2058), Dr. Ronald A. Thisted (Ex. 2060), and Dr. Daniel Wynn (Ex. 2061) to support its contentions.[10]

Oral argument was conducted on November 13, 2019. A transcript is entered as Paper 93 ("Tr.").

We address herein the arguments and evidence set forth in the Papers to the extent necessary to resolve the dispute between the parties.

B. Related Matters

The parties identify the following litigation between the parties involving the '514 patent: *Biogen International GmbH v. Mylan Pharmaceuticals Inc*., C.A. No. 17-cv-116-IMK (N.D. W.Va.). Pet. 2;

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[9] Petitioner also relies on the Declaration of Joel W. Hay, Ph.D. (Ex. 1120) in support of its contentions rebutting portions of Patent Owner's objective indicia evidence that we do not rely upon for this Final Written Decision.

[10] Patent Owner also relies on the Declaration of John C. Jarosz (Ex. 2202) in support of its contentions relating to objective indicia evidence that we do not rely upon for this Final Written Decision.

Paper 11, 3. The parties also identify several other litigations involving the '514 patent. *See* Pet. 2–3; Paper 11, 3.

The '514 patent has also been involved in the following proceedings before the Patent Trial and Appeal Board ("Board"): *Coalition for Affordable Drugs V LLC v. Biogen MA Inc*., IPR2015-01993; *Coalition for Affordable Drugs V LLC v. Biogen MA Inc*., IPR2015-01136; and *Biogen MA Inc., v. Forward Pharma A/S*, Patent Interference 106,023.

C. The '514 patent

The subject matter claimed in the '514 patent is directed to methods of treating patients needing treatment for Multiple Sclerosis (MS). Ex. 1001, 27:59–30:27. The heart of the treatment, and a requirement of every claim, is administering about 480 milligrams (mg) per day of certain fumarates. *Id.* The fumarates are limited to dimethyl fumarate (DMF), monomethyl fumarate (MMF), or their combination. *Id.* Patent Owner markets dimethyl fumarate under the tradename Tecfidera®. *See* PO Resp. 1. Tecfidera® is indicated for the treatment of patients with MS, including relapsing forms of MS (RRMS). Ex. 2003, 7–8, 90.

D. Illustrative Claims

Independent claims 1, 11, 15, and 20, reproduced below, are illustrative of the challenged claims:

> 1. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of
>
> (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and

(b) one or more pharmaceutically acceptable excipients,

wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

Ex. 1001, 27:59–67.

11. A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

Id. at 29:20–23.

15. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject pharmaceutical composition consisting essentially of

(a) a therapeutically effective amount of dimethyl fumarate and

(b) one or more pharmaceutically acceptable excipients,

wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

Id. at 30:1–7.

20. A method of treating a subject in need of treatment for multiple sclerosis comprising treating the subject in need thereof with a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

Id. at 30:22–28.

E. Abbreviations

For convenience, we include a table of abbreviations used in this decision:

DMF	Dimethyl fumarate
BG00012, BG-12, or BG12	Dimethyl fumarate
BID	Twice daily
EDSS	Expanded disability status scale
EMA	European Medicines Agency
MEF	Monoethyl fumarate
MMF	Monomethyl fumarate
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
TID	Three times daily

II. DISCUSSION

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person having ordinary skill in the art ("POSA")

> would have had (1) several years' experience in designing clinical studies to meet regulatory expectations and/or analyzing data from such studies; (2) an advanced degree (PhD, MD, PharmD) and training in clinical pharmacology or experience treating MS; and (3) experience with the administration or formulation of therapeutic agents, their dosing, and the literature concerning drug developmental study and design.

Pet. 10–11.

Patent Owner contends that "Petitioner's proposed definition omits any requirement that a clinician—much less an MS clinician—be included," which is "inconsistent with the subject matter of the claimed invention." PO

Resp. 14. Patent Owner asserts that a person having ordinary skill in the art would have "a medical degree with at least three years of training in neurology and at least three years of clinical experience treating MS." *Id.* (citing Ex. 2061 ¶¶ 35–36).

Having considered the parties' positions and evidence of record, summarized above, we agree with Patent Owner that the claims are limited to methods of treating MS and agree that the definition of a POSA should likewise be limited to those persons having the relevant education and sufficient clinical expertise in treating MS patients. Accordingly, we adopt Patent Owner's definition of a POSA for the purposes of this decision. That said, we discern no appreciable difference in the respective definitions of a POSA as that definition relates to the dispositive issues of this case, discussed below.

We further note that prior art may also demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

For petitions filed before November 13, 2018, we interpret the claims of an unexpired patent that will not expire before issuance of a final written decision using the broadest reasonable interpretation in light of the specification. *See* 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC*

v. Lee, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner submits that none of the terms in the claims of the '514 patent require construction and, instead, all terms take on their plain meaning. Pet. 17. Patent Owner does not present any alternative claim construction arguments. *See generally* PO Resp.

We independently determine that no explicit construction of any claim term is necessary to determine whether Petitioner has shown by a preponderance of the evidence that the claims are unpatentable in this case.

C. Ground 1: Asserted Obviousness of Claims 1–20 over the Combination of the Biogen Press Release and Schimrigk 2004

For the reasons set forth below, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–20 are unpatentable as obvious over the combination of the Biogen Press Release and Schimrigk 2004.

1. Summary of References Relied Upon

a. Biogen Press Release (Ex. 1005)

The Biogen Press Release[11] reports as follows:

> Biogen . . . and Fumapharm AG today announced that a Phase II study designed to evaluate the efficacy and safety of BG-12, an oral fumarate, in patients with relapsing-remitting multiple sclerosis met its primary endpoint. Treatment with BG-12 led to a statistically significant reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI with six months of treatment versus placebo. This Phase II multi-center, double-blind, placebo-controlled study enrolled approximately 250 patients at sites in 10 countries in Europe.

Ex. 1005; Pet. 36.

Petitioner additionally argues that skilled artisans would have understood that the Biogen Press Release reports the results of the study disclosed by Kappos 2005.[12] Pet. 36 (citing Ex. 1002 ¶ 67; Ex. 1003 ¶ 132). Kappos 2005 describes a six month "randomized, double-blind, placebo-controlled, phase II study being conducted at 45 clinical centers in Europe" where daily dosages of 720 mg, 360 mg, and 120 mg were to be tested for efficacy and safety in treating RRMS. Ex. 1015, 2.

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[11] Patent Owner asserts that Petitioner has not established that the Biogen Press Release was a printed publication. PO Resp. 16–17. Because we determine that Petitioner has not met its burden to show unpatentability of the claims based on any asserted ground relying on this document, we need not decide this issue for purposes of this Final Written Decision.

[12] Ex. 1015, L. Kappos et al., *A Randomised, Placebo-controlled Phase II Trial of a Novel Oral Single-Agent Fumarate Therapy, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis*, 252 (Suppl. 2) J. NEUROL. II/148, P574 (2005) ("Kappos 2005").

b. Schimrigk 2004 (Ex. 1006)

Schimrigk 2004 discloses that

> Oral fumarate is an effective and safe therapy for the treatment of psoriasis. Similar to psoriasis, the inflammatory process in multiple sclerosis (MS) is thought to be mediated by a T helper I (THI)-type cytokine reaction due to global immune suppression or a TH2-mediated bystander suppression.

Ex. 1006, 4–5.

Schimrigk 2004 reports the results of a 70-week clinical trial involving the treatment of RRMS with oral fumarate therapy (Fumaderm®). *Id.* at 5. The study consisted of four phases: a 6-week baseline; an 18-week treatment; a 4-week wash-out; and a second 70-week treatment phase. *Id.* Patients received Fumaderm® in dosages that included up to 720 mg/day of DMF[13] in the first treatment phase. *Id.* Patients received Fumaderm® in dosages that included up to 360 mg/day of DMF in the second treatment phase. *Id.* Schimrigk 2004 discloses that "[o]ral fumarate therapy significantly reduced the number and volume of [gadolinium enhancing (Gd+)] lesions over 70 weeks of treatment." *Id.* More specifically, Schimrigk 2004 discloses that

> Significant reductions from baseline in the number of Gd+ lesions were observed starting after week 12 of treatment with fumarate ($p < 0.05$). In addition, there were significant reductions

[13] According to Petitioner, DMF is the most active component of Fumaderm®. Pet. 37; Ex. 1020 (Fumaderm® prescribing information); Ex. 1003 ¶¶ 134, 137, 141–145.

> from baseline in Gd+ lesion volume starting after week 12 ($p < 0.01$).

Id.

c. Schimrigk 2004 Poster (Ex. 1012[14])

According to Petitioner, the Schimrigk 2004 Poster[15] concerns the same study disclosed in Schimrigk 2004. Pet. 37. Petitioner contends that Schimrigk 2004, when read in view of the Schimrigk 2004 Poster, discloses "that the fumarate therapy was effective to treat MS, describing a 'significant reduction in the number of Gd+ lesions . . . following 18 weeks of oral fumarate treatment, with a further reduction after 70 weeks.'" *Id.* (quoting Ex. 1012, 4).

2. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of the Biogen Press Release and Schimrigk 2004. Pet. 34–44. Petitioner contends that the Biogen Press Release discloses that a Phase II study designed to evaluate the efficacy and

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[14] Ex. 1012, S. Schimrigk et al., *A Prospective, Open-Label, Phase II Study of Oral Fumarate Therapy for the Treatment of Relapsing-Remitting Multiple Sclerosis* (2004), available at http://web.archive.org/web/20041021033354/http://www.fumapharm.ch:80/pdf/BG-12_Schimrigk_Poster_Final.pdf ("Schimrigk 2004 Poster").

[15] Patent Owner asserts that Petitioner has not established that the Schimrigk 2004 Poster was publicly available. PO Resp. 17–18 n.7. Because we determine that Petitioner has not met its burden to show unpatentability of the claims based on any asserted ground relying on this document, we need not decide this issue for purposes of this Final Written Decision.

safety of BG-12[16] resulted in "a statistically significant reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI." *Id.* at 36 (citing Ex. 1015).

The Biogen Press Release does not disclose an effective dosage of DMF. As for the dose of DMF used in the study, Petitioner contends that a person of ordinary skill in the art would have understood that the Biogen Press Release reports the results of a study disclosed in Kappos 2005. Pet. 36 (citing Ex. 1002 ¶ 67; 1003 ¶ 132). As noted above, Kappos 2005 describes a six month study testing daily dosages of 720 mg, 360 mg, and 120 mg for efficacy and safety in treating MS. Ex. 1015, 2.

The Biogen Press Release, even when read in view of Kappos 2005, does not indicate which of the tested dosages showed efficacy. In this regard, Petitioner directs our attention to Schimrigk 2004 and the Schimrigk 2004 Poster and contends that those references show "that DMF doses of 720 mg/day, 360 mg/day, and those in between, such as 480 mg/day, were likely to be efficacious to treat MS." Pet. 36. Specifically, Petitioner contends that "[t]he authors reported that the fumarate therapy was effective to treat MS, describing a 'significant reduction in the number of Gd+ lesions . . . following 18 weeks of oral fumarate treatment [where up to 720 mg/day of DMF was administered], with a *further reduction* after 70 weeks[, where

[16] Petitioner contends that a person of ordinary skill in the art would have known that BG-12 referred to DMF monotherapy. Pet. 18 n.2 (citing Ex. 1015 and Ex. 1010). For purposes of this Decision, we will interpret all references to BG-12 or the like to mean DMF.

up to 360 mg/day of was DMF administered].'" *Id.* at 37 (citing Ex. 1012, 4) (emphasis added).[17]

Petitioner contends that, because it was known that DMF was effective in treating MS based on the teachings of Schimrigk 2004, "[s]killed artisans would have been motivated to take the next obvious drug development step: optimize the dose of DMF, taking into account its known side-effect profile, patient compliance issues arising from three times daily dosing, and general principles of drug development." Pet. 37. Petitioner also contends as follows:

> Given these results and the state of the art, skilled artisans would have been motivated to optimize the dose of what was known to be an effective treatment—a process that is part and parcel of routine drug development. Ex. 1002 ¶¶ 132–154; Ex. 1003 ¶¶ 135–148.
>
> Moreover, skilled artisans would be pursuing DMF dose optimization within an established effective range. Prior art pointed to a range of 360 mg/day to 720 mg/day to treat MS.[18] And skilled artisans had achieved success in treating psoriasis with 480 mg/day, providing a particular motivation to pursue that dose when treating MS. Ex. 1002 ¶¶ 136, 147; Ex. 1003 ¶¶ 38,

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[17] We understand Petitioner's argument to be that the study disclosed by the authors of Schimrigk 2004 showed that oral fumarate treatment was shown to be efficacious for both the first treatment period in which up to 720 mg/day of DMF was administered and for the second treatment period in which up to 360 mg/day of DMF was administered. *See* Pet. 36–37; *see also* Tr. 9:22–12:1.

[18] According to Petitioner, "Schimrigk demonstrated the efficacy of Fumaderm® including 360 mg/day and 720 mg/day of DMF . . . in treating RRMS." Pet. 30 (citing Ex. 1002 ¶¶ 47–56, 92–100, 114–116, 128–131, 145 n.5; Ex. 1003 ¶¶ 36–38, 40–42, 61–67, 72–94, 137, 141–147).

> 75-78, 143. For example, in the 1990s, Nieboer demonstrated that 480 mg/day of DMF administered twice daily is an effective daily dose to treat psoriasis. Ex. 1002 ¶¶ 136, 147; Ex. 1003 ¶¶ 78, 143.

Pet. 32.

Regarding a reasonable expectation of success, Petitioner contends that

> Skilled artisans would have also had a reasonable expectation of success in treating MS with 480 mg/day of DMF. Ex. 1002 ¶¶ 144–149; Ex. 1003 ¶¶ 144–147. Schimrigk had shown efficacy of 360 mg/day and 720 mg/day of DMF administered as Fumaderm®, and the January 2006 Press Release confirms efficacy of DMF monotherapy in treating MS. Ex. 1002 ¶¶ 144–149; Ex. 1003 ¶¶ 144–147. These findings, in light of the knowledge that 480 mg/day of DMF could be used to successfully treat psoriasis, would leave little to the skilled artisan's imagination. Ex. 1002 ¶¶ 137–149; Ex. 1003 ¶¶ 144–147. The data all pointed towards successful administration of 480 mg/day of DMF to treat MS. Ex. 1002 ¶¶ 137–149; Ex 1003 ¶¶ 135–148.

Pet. 38.

3. Patent Owner's Contentions

Patent Owner contends that Schimrigk 2004 does not teach that any range of DMF doses (e.g., from 360 to 720 mg/day) were effective to treat MS, "and certainly not 480 mg/day DMF monotherapy." PO Resp. 15. Patent Owner contends that "Schimrigk 2004 is a short abstract reporting the results of an exploratory, open-label study of multiple active oral fumarates (not DMF monotherapy) for the treatment of RRMS." *Id.* at 18 (citing Ex. 1006, 4–5; Ex. 2058 ¶ 25; Ex. 2061 ¶ 37; Ex. 2057 ¶ 21). Specifically, "Schimrigk 2004 administered Fumaderm®, a combination of four active

fumarate ingredients (56% DMF and 44% of three MEF salts) with its six-tablet dose containing 1290 mg of active fumarates (720 mg DMF and 570 mg of the MEF salts)." *Id.* (citing Ex. 1020, 2; Ex. 2058 ¶¶ 45–47; Ex. 2061 ¶¶ 38, 74; Ex. 2057 ¶¶ 22, 35, 39). Thus, according to Patent Owner, "Schimrigk 2004 did not test a DMF-only product and thus could not disclose that 720 mg/day or any other dose of DMF was efficacious for the treatment of MS." *Id.* at 19 (citing Ex. 2058 § VII.A.1; Ex. 2061 ¶ 41; Ex. 2057 § VI.A.2; Paper 12, 15).

4. Analysis

The question before us is whether discovery of the 480 mg/day dose of DMF in a method of treating multiple sclerosis was the result of DMF dose optimization within an established effective range (i.e., doses between 360 mg/day and 720 mg/day). Pet. 27–32; PO Resp. 14–15. In this regard, we recognize that "discovery of an optimum value of a variable in a known process is usually obvious." *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1368 (Fed. Cir. 2007); *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'" (quoting *Aller*, 220 F.2d at 456)). However, for the optimization of a dosage within an established

range to be obvious, the asserted prior art must teach that such an established effective range was known.

As mentioned above, the Biogen Press Release, even when read in view of Kappos 2005, does not indicate which of the tested dosages for BG-12 (DMF monotherapy) showed efficacy. Thus, the Biogen Press Release fails to establish any effective dose range for DMF monotherapy.

To support its position that a person of ordinary skill in the art would have known that the 360 mg/day and 720 mg/day doses of DMF were efficacious, Petitioner relies on Schimrigk 2004. *See, e.g.*, Pet. 30, 38. Schimrigk 2004, however, does not cure that deficiency of the Biogen Press Release because Schimrigk 2004 does not describe or suggest a DMF monotherapy in any particular dose. Ex. 2057 ¶¶ 22, 35, 39. Rather, Schimrigk 2004 discloses that patients were treated with oral fumarate therapy, known as Fumaderm. Ex. 1006, 5. Fumaderm contains "approximately 44% MEF salts and only 56% DMF," where MEF refers to monoethyl fumarate compounds, compounds that are not encompassed by the challenged claims. Ex. 2058 ¶¶ 46–47; *see also* Ex. 1008, 3 (listing the components of Fumaderm). More specifically, Fumaderm contains DMF and three MEF salts—calcium MEF, zinc MEF, and magnesium MEF—each of which is an active ingredient. Ex. 2061 ¶ 74; Ex. 1037[19], 109–120 (European Medicines Agency concluding that "DMF and the MEF salts are chemically distinct active substances" and that "dimethyl fumarate is

[19] Ex. 1037, European Medicines Agency, *Assessment Report, Tecfidera* (Nov. 26, 2013) ("EMA Report").

different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate. Therefore, the active substance of Tecfidera, dimethyl fumarate, is a new active substance."). Thus, we find that Schimrigk 2004 does not teach or suggest anything about the effectiveness of any individual fumarate so as to guide a person of ordinary skill in the art to an effective dose range for DMF monotherapy.[20]

Having considered the parties' positions and evidence of record, summarized above, we determine that the evidence relied on by Petitioner does not support Petitioner's position that a person of ordinary skill in the art would have understood that "doses between 360 mg/day and 720 mg/day were likely to be efficacious doses, and, in particular, 480 mg/day was likely to be an efficacious dose." Pet. 38–39 (citing Ex. 1002 ¶¶ 125–154; Ex 1003 ¶¶ 132–148). Rather, we are persuaded by Patent Owner's arguments and evidence that "[t]he presence of multiple active agents in Fumaderm® precludes extrapolation of Schimrigk 2004's results to any dose of DMF monotherapy." PO Resp. 19; Ex. 2058 ¶¶ 46–48, 51; Ex. 2057

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[20] Petitioner argues on Reply that "Schimrigk's Fumaderm® efficacy finding is akin to DMF monotherapy" because "DMF has long been known to [be the] most active Fumaderm® component." Reply 5 (citing Ex. 1002 ¶¶ 132–140, 145 n.4 n.5; Ex. 1121 ¶¶ 200–204; Ex. 1023; Ex. 1024). Petitioner does not dispute, however, Patent Owner's contention that there are components in Fumaderm other than DMF. Patent Owner's expert testimony in this regard is consistent with the other record evidence. Ex. 2058 ¶ 46 ("Fumaderm® tablets contained approximately 44% MEF salts and only 56% DMF."); *see also*, Ex. 1008, 3:12–24 (same).

¶¶ 22, 35, 37–29; Ex. 2062, 33:1–25. We, thus, determine that Petitioner has failed to establish that a person of ordinary skill in the art would have relied on the combination of the Biogen Press Release and Schimrigk 2004 to optimize the dose for DMF for the treatment of MS within an established effective range because the art does not support a finding that any such range was known. Ex. 2058 ¶¶ 50, 69–70, 92–95, 116–147; Ex. 2061 ¶¶ 56–58; Ex. 2057 ¶¶ 37–42, 65, 67–84. Having failed to establish the facts predicate to its articulated theory of obviousness, Petitioner's obviousness challenge to claims 1–20 also fails.

D. Ground 2: Asserted Obviousness of Claims 1–20 over the Combination of Kappos 2006 and Schimrigk 2004

For the reasons set forth below, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–20 are unpatentable as obvious over the combination of Kappos 2006 and Schimrigk 2004.

1. Summary of Additional Reference Relied Upon

a. Kappos 2006 (Ex. 1007)

Kappos 2006[21] describes results of a Phase II trial that treated MS patients with 120, 360, and 720 mg/day of a drug identified as BG00012

[21] Patent Owner asserts that Kappos 2006, along with related Exhibits 1016 and 1046, are not available as prior art against the challenged claims because they describe inventor Dr. O'Neill's own work. *See* PO Resp. 4–13; Ex. 2097; Ex. 2098; Ex. 2099; Ex. 2100. Because we determine that Petitioner has not met its burden to show unpatentability of the claims based on any asserted ground relying on these documents, we need not decide this issue for purposes of this Final Written Decision.

(BG12). Ex. 1007, 27. The relevant portion of Kappos 2006 provides as follows (emphasis added):

> Objective: To determine the efficacy of three dose levels of *BG00012*, a novel oral fumarate preparation, on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with *relapsing-remitting multiple sclerosis (RRMS)*.
>
> Methods: This was a randomised, double-blind, placebo-controlled clinical trial of BG00012 in patients with RRMS. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have had either ≥ 1 relapse within 12 months prior to randomisation or gadolinium-enhancing (Gd +) lesions on cranial MRI at screening. Patients were assigned to four treatment groups and *received BG00012 capsules 120 mg by mouth (PO) once daily (120 mg/day), 120 mg three times daily (360 mg/day), 240 mg three times daily (720 mg/day), or placebo for 24 weeks*. The treatment period was followed by a 24-week dose-blinded safety-extension period during which all patients received BG00012. The primary end point was the total number of Gd+ lesions over four MRI scans at weeks 12, 16, 20, and 24 (calculated as the sum of the four scans). Secondary end points included the cumulative number of new Gd+ lesions from week 4 to week 24 and the number of new/enlarging T2-hyperintense lesions at week 24. Additional end points included the number of new T1-hypointense lesions at week 24, relapse rate, and disability progression as measured by EDSS.
>
> Results: A total of 257 patients were enrolled in the study; 64 patients each were randomly assigned to receive one of the three BG00012 doses and 65 patients to placebo. *Approximately 90% of patients completed the 24-week treatment period. BG00012 (720 mg/day) significantly reduced the mean number of new Gd+ lesions (the primary end point) compared with placebo.* In addition, BG00012 reduced the cumulative number of new Gd+ lesions, the number of new/enlarging

> T2-hyperintense lesions, and the number of new T1-hypointense lesions compared with placebo.
>
> Conclusion: BG00012 significantly reduces brain lesion activity, *in a dose-dependent manner*, as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 1007, 27 (emphases added).

2. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006 and Schimrigk 2004. Pet. 44–48. Petitioner contends that Kappos 2006 "explicitly discloses that 720 mg/day of DMF monotherapy is an effective MS treatment" and further discloses that "[DMF] significantly reduces brain lesion activity, in a dose-dependent manner." Pet. 44–45 (citing Ex. 1007, 27). For the same reasons set forth in Ground 1, Petitioner contends that Schimrigk 2004 teaches or suggests efficacy in the treatment of MS at a dose of 360 mg/day of DMF. *Id.*

Additionally, regarding the 360 mg/day dose, Petitioner contends that a person of ordinary skill in the art would have understood at the time of the invention that Kappos 2006 actually shows that the 360 mg/day dose was an efficacious dose. *Id.* at 46. Specifically, Petitioner contends that,

> in May 2006, Kappos presented the results of his research to skilled artisans at a leading neurology conference. Ex. 1046[22]. In his slides, Kappos revealed that the patients who had been

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[22] Ex. 1046, L. Kappos et al., *Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase II Study* (16th Meeting of the European Neurological Society, May 30, 2006) ("Kappos 2006 Presentation").

> treated with 360 mg/day of DMF had baseline disease activity that was markedly higher than those patients receiving 720 mg/day, 120 mg/day, and placebo. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–170. Skilled artisans would have immediately recognized that when assessing whether the 360 mg/day dose was effective, a correction for the higher baseline disease activity in that group would be necessary. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–172. Skilled artisans would have at a minimum questioned the efficacy conclusions reported for the 360 mg/day dose, and could have performed easy calculations suggesting that 360 mg/day was efficacious. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–179.

Id. Thus, in addition to providing the statement that DMF was effective in treating RRMS in a dose-dependent manner, Petitioner contends that a person of ordinary skill in the art would have been aware of the data contained in the Kappos 2006 Presentation by the same author (Ex. 1046, 8–29) and "would have immediately recognized from the Kappos 2006 slides that MS patients who received 360 mg/day DMF during the study had significantly higher disease activity at the start of the study (baseline) than the patients in the other treatment groups." Pet. 54–55 (citing Ex. 1002 ¶¶ 178–180, 203–204; Ex. 1003 ¶¶ 169–172, 207–209).

To support its position that a person of ordinary skill in the art would have immediately recognized the data flaw in Kappos 2006, Petitioner directs our attention to the data presented in the Kappos 2006 Presentation. Pet. 9–10. In particular, Petitioner contends that the data confirm DMF's dose-dependency because POSAs would have immediately noticed the heightened baseline disease activity in the 360 mg/day group. Ex. 1002 ¶ 179; Ex. 1003 ¶ 170; Ex. 1121 ¶ 149.

Petitioner's expert, Dr. Benet, testifies that

> 169. . . . [T]he [Kappos 2006 Presentation] disclosed that the mean number of baseline Gd+ lesions for the groups was as follows: placebo group = 0.8 (±1.37 SD), 120 mg/day group= 1.2 (±1.83 SD), 360 mg/day group= 2.5 (±4.22 SD) and 720 mg/day group = 1.2 (±3.52 SD) ("SD"= Standard Deviation). [Ex. 1046, 17].
>
> 170. It is my opinion that, based on the data presented in the Kappos 2006 Presentation, skilled artisans would have *immediately recognized the major discrepancy in the mean number of baseline Gd+ lesions in the patient group treated with 360 mg/day of DMF* because the mean number of baseline Gd+ lesions for the 360 mg/day group is strikingly higher than the mean number of baseline lesions reported for all other treatment groups. *Id.*
>
> 171. Thus, skilled artisans would appreciate that the over three-fold difference in mean number of baseline Gd+ lesions for the 360 mg/day treatment group compared to the mean number of baseline Gd+ lesions in the placebo group (i.e., 2.5 compared to 0.8, respectively) would significantly influence the outcome of the study, particularly given that the primary endpoint of the study was the total number of new Gd+ lesions on MRI scans performed at weeks 12, 16, 20, and 24. *Id.* at 14, 17. In my opinion, skilled artisans would be very skeptical of the results indicating that treatment with 360 mg/day of DMF did not reach statistical significance. Ex. 1016[23] ([Biogen] May 2006 Press Release).
>
> 172. In my opinion, skilled artisans would notice this discrepancy and would be able to easily normalize the data to adjust for the imbalance of baseline Gd+ lesions and generate a

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[23] Ex. 1016, Biogen News Release, *Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting Multiple Sclerosis; Treatment with BG-12 Led to Statistically Significant Reductions in MRI Measures* (May 30, 2006) ("Biogen May 2006 Press Release").

> rough estimation of the dose-response curve for DMF. *Based solely on the data provided in the Kappos 2006 Presentation, skilled artisans would have the ability to normalize the data and adjust for the baseline Gd+ lesions in a variety of ways*.
>
> 173. For example, skilled artisans could normalize the data to adjust for the baseline Gd+ lesions and re-display the data as the mean number of new Gd+ lesions normalized by *subtracting* the mean number of baseline Gd+ lesions . . . .
>
> 174. A bar graph of the resulting data indicates that there is a dose-response relationship between the 120 mg/day, 360 mg/day and 720 mg/day doses of DMF. . . .
>
> 175. Additionally, in my opinion, skilled artisans could also normalize the data by redisplaying the data as the mean number of new Gd+ lesions per scan *divided* by the mean number of baseline Gd+ lesions. . . .
>
> 177. Thus, skilled artisans, after correcting for the discrepancy seen with the mean number of baseline Gd+ lesions, would be skeptical of the Kappos Phase II study results with respect to the purported lack of efficacy of the 360 mg/day dose, and would be motivated to optimize the dose of DMF.

Ex. 1003 ¶¶ 169–177 (emphases added).

Similarly, Petitioner's expert, Dr. Corboy, testifies that

> 179. The data on the slides [from the Kappos 2006 Presentation] show that the patients in the group that received 360 mg/day of DMF were experiencing more active disease at baseline. The slide titled "Baseline Patient Characteristics" notes the baseline number of Gd+ lesions in each of the treatment groups. The placebo group had an average of 0.8 Gd+ lesions, the 120 mg/day group had 1.2 Gd+ lesions, the 720 mg/day group had 1.2 Gd+ lesions, and the 360 mg/day group had 2.5 Gd+ lesions. Ex. 1046 at 17. The significantly higher mean number of Gd+ lesions at baseline indicates a higher disease activity level in the patients in the 360 mg/day group. Given the higher baseline disease activity present in patients in the 360 mg/day

> group, skilled artisans would have immediately recognized that the Kappos efficacy conclusions with respect to that group did not accurately reflect the data and required correction.
>
> 180. Reviewing the Kappos slides in total, including the higher baseline disease activity in the 360 mg/day group, skilled artisans would have expected that the 360 mg/day DMF dose was likely an efficacious dose. There are several ways in which skilled artisans could calculate the effect that the high baseline disease activity had on the efficacy results of the 360 mg/day group. Regardless of how the calculation is performed, however, skilled artisans would have understood that the baseline data indicated that a correction needed to be made. . . .
>
> 181. . . . While the [Biogen May 2006 Press Release (Ex. 1016)] reported that the 360 mg/day DMF dose did not show statistically significant efficacy, the baseline disease activity data in the Kappos slides immediately called that conclusion into question, and suggested that dose likely *was* efficacious. . . .

Ex. 1002 ¶¶ 179–181.

Thus, according to Petitioner, a person of ordinary skill in the art would have appreciated the flaw in reporting the results of the Kappos 2006 phase II study and would have understood from the Kappos 2006 Presentation that 360 mg/day was also an efficacious dose. Pet. 58 (citing Ex. 1002 ¶¶ 139–140, 209–211; Ex. 1003 ¶¶ 133–134, 220–222; Ex. 1004 ¶¶ 24, 27–28). Petitioner contends that, "[w]ith doses of 720 mg/day and 360 mg/day both demonstrating efficacy, skilled artisans would have been motivated to optimize the dose of DMF to account for side effects, patient compliance, and general drug development design principals . . . ." *Id.* at 45. Petitioner further contends that

> Skilled artisans would have likewise had a reasonable expectation that 480 mg/day would work: 480 mg/day fell

> between two doses of DMF that had demonstrated efficacy as reported in Kappos 2006 and the Schimrigk 2004 study, and had exhibited efficacy in treating psoriasis. Ex. 1002 ¶¶ 167–177; Ex. 1003 ¶¶ 160–168.

Id.

3. Patent Owner's Contentions

Patent Owner contends that the evidence relied upon by Petitioner only establishes the efficacy of the 720 mg/day dose of DMF, and thus does not establish an effective DMF dose range. PO Resp. 25–26. In particular, with reference to Kappos 2006, Patent Owner contends that

> Kappos 2006, a four-paragraph abstract, reports that "BG00012 (720 mg/day [of DMF]) significantly reduced the mean number of new Gd+ lesions (the primary end point) compared with placebo." Ex. 1007, 27. It identifies no other dose as distinguishable from placebo and identifies no effective dose range. Ex. 1007, 27; Ex. 2057 ¶¶ 28, 67–68; Ex. 2058 ¶¶ 35, 92–95; Ex. 2060 ¶¶ 23–34; Ex. 2061 ¶¶ 47, 57. . . . Kappos 2006's reference to a "dose-dependent manner" similarly does not provide any information regarding an effective dose range, and a POSA would not have understood that this refers to any clinical response at the lower doses studied. Ex. 2058 ¶¶ 116, 167; Ex. 2062, 32:10–23 (Dr. Benet agreeing that "a dose response doesn't imply that all doses have efficacy"); Ex. 2057 ¶ 77.

PO Resp. 25–26. Thus, according to Patent Owner,

> Petitioner's dose-optimization theory fails because there was, at most, only a single DMF-monotherapy dose (720 mg/day) shown to be potentially effective. There was no range to be optimized. And a POSA would not have had a motivation or reasonable expectation of success to use DMF-monotherapy doses lower than 720 mg/day to effectively treat MS.

PO Resp. 26.

Patent Owner additionally disputes Petitioner's contention that a person of ordinary skill in the art would have understood at the time of the invention that the data presented in the Kappos 2006 Presentation indicated that the 360 mg/day dose was an efficacious dose. PO Resp. 27–28, 31–37. Relying on the testimony of its experts, Dr. Duddy and Dr. Thisted, Patent Owner provides a list of challenges to Dr. Benet's post hoc analysis of the data in the Kappos 2006 Presentation. *Id.* at 31–37. Specifically, Patent Owner first contends that Dr. Benet's assumptions ignore the transient nature of Gd+ lesions, which, as Dr. Duddy explains, appear on MRI scans for only up to 6 weeks. *Id.* at 32 (citing Ex. 2058 ¶¶ 18, 132; Ex. 1002 ¶ 43; Ex. 2060 ¶ 42; Ex. 2061 ¶ 22). The transient nature of Gd+ lesions is relevant "[b]ecause the primary endpoint in the Kappos presentation was the total number of new Gd+ lesions measured on MRI scans at weeks 12, 16, 20, and 24," therefore Dr. Benet, in his post hoc analysis of the data "is subtracting or dividing out baseline Gd+ lesions already excluded from the primary endpoint data." *Id.* (citing Ex. 1046, 14, 19; Ex. 2058 ¶ 142).

Second, Patent Owner contends that Dr. Benet's calculations fail "to consider the large standard deviations reported for the Gd+ baseline data." *Id.* at 33 (citing Ex. 1046, 17; Ex. 2060 ¶¶ 49–53, 59; Ex. 2061 ¶ 61).

Third, Patent Owner contends that Dr. Benet's calculations

> improperly mix and match the average baseline data for the enrolled group (64 patients in the 360 mg/day group) with average primary endpoint data from the smaller group of patients who actually completed the study (56 patients for the 360 mg/day group). Ex. 2058 ¶¶ 129–130; Ex. 2060 ¶¶ 55–64; Ex. 2061 ¶ 64; Ex. 2057 ¶¶ 79–81. Dr. Benet's assumption that the enrolled

> patient baseline average is representative of the group that completed the study despite the ~12% dropout rate is baseless.
>
> Because of the large standard deviation (>150%) for the average baseline Gd+ lesions of the 360 mg/day group, at least one outlier patient entered the study with significantly more than the mean 2.5 baseline Gd+ lesions. Ex. 1046, 17; Ex. 2060 ¶¶ 53, 59–62; Ex. 2058 ¶¶ 129–130; Ex. 2057 ¶ 81; Ex. 2061 ¶ 64. If an outlier patient was among the eight patients that dropped out before completing the study, the average baseline value for the 56-patient group that completed the study would be much lower than for the 64-patient starting group. *Id.* Consequently, Dr. Benet's analysis would skew the results, overstating an effect for the 360 mg/day group. Ex. 2060 ¶ 59–62; Ex. 2058 ¶¶ 129–130; Ex. 2057 ¶ 81; Ex. 2061 ¶ 64.

PO Resp. 33–34 (footnote omitted).

Fourth, Patent Owner contends that "Dr. Benet's hindsight-driven calculations change the study design in a way that 'is not a valid trial design for a dose-finding study,'" and are therefore without clinical relevance. *Id.* at 34–35 (quoting Ex. 2058 ¶ 126; citing *id.* ¶¶ 124–128; Ex. 2061 ¶¶ 62–65).

Fifth, Patent Owner contends that Dr. Benet's calculations are arbitrary and inconsistent because he used different mathematical assumptions for his division and subtraction calculations without justification. *Id.* at 35 (citing Ex. 2060 ¶¶ 42–48). In particular, Patent Owner contends that,

> To adjust the primary endpoint data in his subtraction analysis, Dr. Benet takes the *total* number of new Gd+ lesions from four MRI scans making up the primary endpoint and then subtracts the baseline average. Ex. 2060 ¶¶ 43–48. But for his division analysis, he divides a *single-scan average* of the four MRI scans by the baseline average. Ex. 2060 ¶¶ 49–52. . . . [I]f

> Dr. Benet had consistently used the single-scan average of the primary endpoint for both calculations, his "normalization" subtraction approach leads to negative lesions, which is not physically possible, and there is no "dose-response relationship between the 120 mg/day, 360 mg/day and 720 mg/day dose," as Dr. Benet contends. Ex. 1003, ¶ 212; Ex. 2058 ¶ 18; Ex. 2060 ¶¶ 45–48.

PO Resp. 36 (emphasis Patent Owner's).

Thus, according to Patent Owner, Dr. Benet's post hoc calculations based on the data presented in the Kappos 2006 Presentation cannot be relied upon to show that the 360 mg/day dose was efficacious.

4. Analysis

As in Ground 1, a factual dispute between the parties is whether the 360 mg/day dose of DMF was known at the time of the invention to be efficacious in the treatment of MS. In this Ground, Petitioner relies on the same teachings of Schimrigk 2004 to support its position that Schimrigk 2004 discloses efficacy in MS of a 360 mg/day dose of DMF administered as Fumaderm. Pet. 45. For the same reasons set forth above in Section II.C.4., however, we determine that Schimrigk 2004 discloses effective doses for the product Fumaderm only, where Fumaderm is a different drug product containing four chemically distinct active substances, only one of which is the DMF monotherapy encompassed by the challenged claims. Ex. 1006, 5; Ex. 2058 ¶¶ 46–47; Ex. 1008, 3; Ex. 2061 ¶ 74; Ex. 1037, 109–120. Accordingly, we are not persuaded that Schimrigk 2004 can be relied upon to teach or suggest a DMF monotherapy in any particular dose. Ex. 2057 ¶¶ 22, 35, 39. We incorporate here our findings above regarding the disclosure of Schimrigk 2004 in this regard.

We are also not persuaded that a person of ordinary skill in the art would have understood Kappos 2006 to teach efficacy in treating MS with a 360 mg/day dose of DMF. Rather, for the reasons set forth by Patent Owner, which we have summarized above and adopt here (PO Resp. 31–37 (section IV.B.2.b)), we are persuaded that a person of ordinary skill in the art would not have found the post hoc calculations of Dr. Benet to be reliable in ascertaining whether the 360 mg/day of DMF was efficacious. In particular, we credit the testimony of Dr. Thisted and Dr. Duddy that the endpoint of the Kappos 2006 study was intended to measure the effectiveness of the drug regimen at suppressing new Gd+ lesions, and thus, subtracting, for example, the number of temporary lesions present at an earlier time is not relevant to the outcomes measured by the study. Ex. 2060 ¶¶ 42–54; Ex. 2058 ¶¶ 120–126 (Dr. Benet's proposed method "completely changes the trial design.").

We also credit the testimony of Dr. Thisted and Dr. Duddy that it would not have been possible to conclusively "correct" for a purported baseline variation using the data in Kappos 2006 and the Kappos 2006 Presentation because the results shown relate only to patients who finished the study, and the baseline data relates to all patients who began the study. Ex. 2058 ¶ 130; Ex. 2060 ¶¶ 55–64. For example, Dr. Duddy testifies that the data in the Kappos 2006 Presentation shows that there were "fewer subjects in each of the treatment groups that were scanned for the secondary endpoint (new Gd+ lesions at weeks 4-24) listed on Slide 36 than the primary endpoint (new Gd+ lesions at weeks 12-24) on Slide 35." *Id.* (citing Ex. 1046, 19 (slide 35), 20 (slide 36)). Thus, as Dr. Duddy explains,

> Whether these missing scans were due to patient discontinuation, which occurred, or deviations from the protocol is not clear, and it is further unclear whether the same group of patients are included at each time point. The presentation does not suggest that the authors attempted to impute missing data or model best- and worst-case scenarios for the missing scans. In particular, it is not known from the Kappos 2006 slides whether the outliers dropped out or were part of the final efficacy group. As a consequence, one cannot employ the crude post hoc calculations that Dr. Benet proposes to correct for a purported baseline variation when a loss of one or two high baseline individuals during the study could remove the purported imbalance without any change in the observed effect from the drug.

Ex. 2058 ¶ 130.

In view of the above, we are not persuaded that the preponderance of evidence establishes that it was known or would have been understood by a person of ordinary skill in the art that the 360 mg/day dose of DMF was efficacious in treating MS. Accordingly, we are not persuaded by Petitioner's contention that skilled artisans would have been motivated to optimize the dose of DMF within an established effective dose range.[24]

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[24] Petitioner asserts in its Reply that "[e]ven if, however, 720 mg/day of DMF had been the only known efficacious daily DMF dose, POSAs would not stop there. Instead, POSAs would have been motivated to lower the DMF dose to account for known side effects." Reply 2–3. Petitioner did not make this argument in Ground 2 of the Petition, however, and we find that it is untimely. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331 (Fed. Cir. 2019) ("an IPR petitioner may not raise in reply 'an entirely new rationale' for why a claim would have been obvious."); quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (Petitioner is required to "identif[y], in writing and with particularity. . . the grounds on which the challenge to each

Having failed to establish the facts predicate to its articulated theory of obviousness, Petitioner's obviousness challenge to claims 1–20 also fails.

E. Ground 3: Asserted Obviousness of Claims 1–20 over the Combination of Kappos 2006 and WO '342

For the reasons set forth below, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–20 are unpatentable as obvious over the combination of Kappos 2006 and WO '342.

1. Summary of Additional Reference Relied Upon

a. WO '342 (Ex. 1008)

WO '342 discloses "controlled release pharmaceutical compositions comprising fumaric acid ester(s) as active substance(s)." Ex. 1008, Abstract. WO '342 discloses that the compositions of the invention are suitable for use in the treatment of a variety of autoimmune diseases, including multiple sclerosis. *Id.* at 37:25–38:9.

With regard to dosages, WO '342 provides the following guidance:

> The daily dosage of the controlled release pharmaceutical composition according to the invention that is administered to treat a patient depends on a number of factors among which are included, without limitation, weight and age and the underlying causes of the condition or disease to be treated, and is within the skill of a physician to determine. In one aspect of the invention the daily dosage can be e.g. from 240 to 360 mg active substance given in one to three doses, in another aspect from 360 to 480 mg active substance given in one to three doses, in another aspect 480 to 600 mg active substance given in one to three doses, in another aspect 600 to 720 mg active substance given in one to

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claim is based" in the petition). We, thus, do not consider this theory in rendering our Final Written Decision.

> three doses, in another aspect 720 to 840 mg active substance given in one to three doses, in another aspect 840 to 960 mg active substance given in one to three doses and in yet another aspect 960 to 1080 mg active substance given in one to three doses.

Id. at 36:13–23.

2. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006 and WO '342. Pet. 48–50. As in Ground 2, Petitioner relies on Kappos 2006 for its disclosure that the dose of 720 mg/day DMF is efficacious for MS treatment. *Id.* at 48. Additionally, Petitioner contends that WO '342 suggests the use of the 480 mg dose of DMF in the treatment of autoimmune disease, such as MS. *Id.* at 48–49.

Petitioner provides the following rationale for why a person of ordinary skill in the art would have sought to combine the teachings of Kappos 2006 and WO '342:

> Specifically, Petitioner contends that
>
> > Based on Kappos 2006 in view of WO '342, in light of the state of art, skilled artisans would have understood that (1) DMF monotherapy was an effective MS treatment, (2) the side-effect profile, drug development theory, and patient compliance issues were reasons to optimize the daily dose of DMF, (3) doses between 360 mg/day and 720 mg/day were likely to be efficacious, and (4) 480 mg/day was a likely efficacious DMF dose to treat MS. Ex. 1002 ¶¶ 183–188; Ex. 1003 ¶¶ 181–188. Therefore, it would have been obvious to one of ordinary skill in

> the art to administer 480 mg/day of DMF for the treatment of MS.

Pet. 49.

3. Patent Owner's Contentions

Patent Owner contends that "WO '342 never distinguishes MS from the laundry list of conditions and never links it to any particular active ingredient or dose." PO Resp. 44 (citing Ex. 1008, 39–41; Ex. 2061 ¶¶ 102–106, 111–113; Ex. 2058 ¶¶ 36–38, 107–108).

Patent Owner further contends that both the Board and Federal Circuit found that WO '342 "does not indicate 480 mg/day is a therapeutically effective dose with respect to any condition or disease or is otherwise of any particular significance with respect to MS." *Id.* at 43 (quoting Ex. 2030, 22 (Decision in related Interference 106,023); citing *FWP IP APS v. Biogen MA Inc*., 749 F. App'x at 973).

Patent Owner also contends that objective evidence, including unexpected results, demonstrate the patentability of the challenged claims. *Id.* at 49–61. Patent Owner further asserts "[t]here is presumptive nexus" because Tecfidera embodies the challenged claims. *Id.* at 55–56.

4. Analysis

a. The dose of DMF in the treatment of MS was recognized as a result-effective variable, the optimization of which is not inventive

"Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc*., 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Aller*, 220 F.2d at 456); *see also KSR Int'l Co. v.*

Teleflex, 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."). This rule is limited to cases in which the optimized variable is a "result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977).

The dispute between the parties is centered on the question of whether treating MS with DMF at a dose of 480 mg/day would have been obvious. Petitioner sets forth the foregoing teachings of Kappos 2006 and WO '342 and provides a detailed discussion explaining how each claim limitation is disclosed in the combination of references. Pet. 48. In particular, Kappos 2006 discloses that 720 mg/day of DMF monotherapy is an effective MS treatment. Ex. 1007, 27. WO '342 suggests a daily dosage of 480 to 600 mg of fumaric acid esters in one to three doses for treatment of autoimmune diseases, such as MS. Ex. 1008, 37:25–38:9. Additionally, it was known that 480 mg/day DMF exhibited efficacy in treating psoriasis, and thus was known to be a safe dose. Ex. 1002 ¶¶ 167–177; Ex. 1003 ¶¶ 160–168.

Moreover, Kappos 2006 discloses that DMF functions in a dose-dependent manner. Ex. 1007, 27. Accordingly, a person of ordinary skill in the art would have understood that the dose of DMF is a result-effective variable in the treatment of MS. Ex. 1002 ¶ 94.

Having considered the parties' positions and evidence of record, summarized above, we are persuaded that the combination of Kappos 2006 and WO '342 teaches or suggests that (1) DMF monotherapy was an effective MS treatment at a 720 mg/day dose and (2) the side-effect profile,

drug development theory, and patient compliance issues were reasons to optimize the daily dose of DMF. Here, we credit the testimony of Dr. Corboy that DMF had well-known side effects (including flushing and gastrointestinal issues), and thus a person of ordinary skill in the art would have been motivated to optimize DMF dosing in MS in order to "minimize DMF's well-known, dose-dependent side effects and enhance patient adherence to therapy." Ex. 1002 ¶ 181. Accordingly, we determine that the evidence of record supports Petitioner's contention that a person of ordinary skill in the art would have been motivated to optimize the daily dose of DMF with a reasonable expectation of success. *See In re Boesch*, 617 F.2d at 276 ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art [and obvious.]").

b. Patent Owner's evidence of unexpected results is sufficient to overcome Petitioner's obviousness challenge

Obviousness may be rebutted, however, "where the results of optimizing a variable, which was known to be result effective, [are] unexpectedly good." *In re Antonie*, 559 F.2d at 620.[25] In this case, Patent

[25] We also agree with Patent Owner's assertion that there is a presumptive nexus, because the "objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." *WBIP, LLC v. Kohler Co*., 829 F.3d 1317, 1329 (Fed. Cir. 2016) (quotations omitted). Petitioner does not allege a lack of nexus between the claimed method and Patent Owner's evidence offered as evidence of unexpected results. *See generally* Pet. and Reply. We independently determine that a sufficiently close relationship exist between the claimed dose and the dose tested for DMF monotherapy to establish nexus with regard to Patent Owner's evidence of unexpected results.

Owner provides argument and evidence in support of its position that the 480 mg/day dose had an unexpected magnitude of efficacy as compared to a much higher 720 mg/day dose. PO Resp. 49–55. Specifically, Patent Owner directs us to the results of two post-filing date Phase III trials for DMF, DEFINE (Ex. 1038) and CONFIRM (Ex. 1039), which investigated both 480 mg/day and 720 mg/day doses of DMF in placebo-controlled, double-blinded studies. PO Resp. 50. Patent Owner additionally relies on the testimony of Drs. Duddy (Ex. 2058), Thisted (Ex. 2060), and Wynn (Ex. 2061) to argue unexpected results.

DEFINE compares the results of treatment with DMF at 240 mg three times a day (720 mg/day), DMF at 240 mg twice a day (480 mg/day) and placebo. Ex. 1038, 1. CONFIRM compares the same doses of DMF with placebo and additionally with an active agent for MS treatment, glatiramer acetater. Ex. 1039, 1. Patent Owner argues that "DEFINE and CONFIRM, established the surprising results that a 480 mg/day dose of DMF had high efficacy in treating MS similar to the much higher 720 mg/day dose for almost every endpoint measured." PO Resp. 49 (citing Ex. 2058 ¶¶ 135–187; Ex. 2061 ¶¶ 124–136; Ex. 2060 ¶¶ 89–113).

Patent Owner directs us to its Figure 2 which is said to be based upon data pooled from DEFINE and CONFIRM. PO Resp. 50–51; Ex. 2058 ¶ 172. Figure 2 graphically compares the relative effects of doses of 480 mg/day (circle) and 720 mg/day (triangle) to that of placebo. PO Resp. 50–51. We reproduce Figure 2 below:

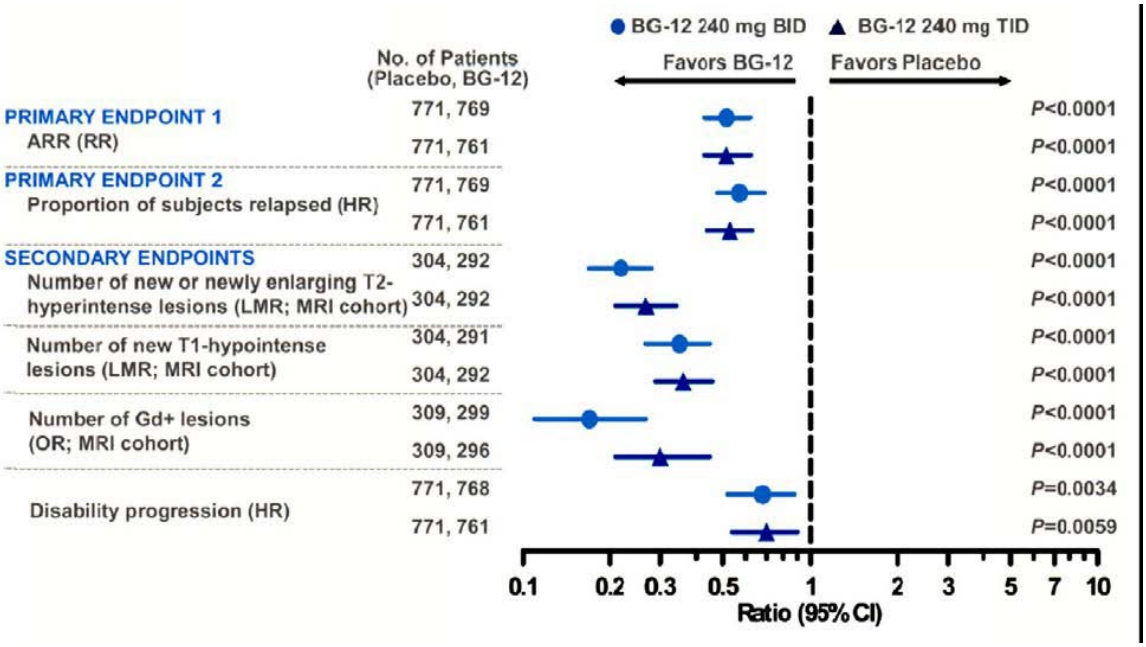

Figure 2, reproduced from Patent Owner's Response (PO Resp. 50–51) depicts the ratio of the effects on MS patients of treatment with 480 mg/day and 720 mg/day to that of placebo. *See also* Ex. 2058 ¶ 172; Ex. 2061 ¶ 133. The figure shows the ratios of the magnitude of the identified outcome to the magnitude resulting from administration of placebo. Ex. 2058 ¶ 172; Ex. 2061 ¶¶ 133–134. The dashed line, showing a value of "1," indicates no difference in effect of the treatment between the tested drug and placebo. Ex. 2061 ¶¶ 133–134. Values to the left of the dashed line show effects that are better than placebo. *Id.* The data shows that the ratio for most of the effects are very similar for 480 mg/day and 720 mg/day on every outcome including efficacy. Ex. 2058 ¶ 172; 2060 ¶ 97; Ex. 2061 ¶¶ 133–134.

All three of Patent Owner's experts testify that one skilled in the art would have expected the efficacy of 480 mg/day to be closer to that of 360 mg/day, a dose which had not been shown to have a statistically

significant effect, than to the 720 mg/day dose described in Kappos 2006. For example, Dr. Thisted testifies that:

> Both the DEFINE and CONFIRM studies show that the therapeutic effects on brain lesions at 480 mg/day are essentially the same as those seen at 720 mg/day. It is stunning and unexpected to see, in two large independent studies, that increasing an ineffective dose (360 mg/day) by a small amount (120 mg/day) produces a strong therapeutic effect, and that a further, larger dose increase (to 720 mg/day) produces virtually no additional therapeutic benefit.

Ex. 2060 ¶ 100.

Additionally, governmental health agencies, the FDA and EMA, also concluded that the 480 and 720 mg/day doses had "comparable efficacy" and statistically significant effects of "similar direction and magnitude," respectively. Ex. 2003, 8; Ex. 1037, 75; *see also* Ex. 2004, 48; Ex. 2066, 24–25; Ex. 2060 ¶¶ 104–108; Ex. 1011, 10. That comparison was sufficient for FDA approval of 480 mg/day DMF treatment for MS. Ex. 2003, 8 ("Since the 240 mg tid dose [720 mg/day] offered no additional efficacy to the 240 mg bid dose [480 mg/day], I recommend approval of the 240 mg bid dose only."); Ex. 2066, 26.

When we consider together all of Patent Owner's evidence in support of its position of the existence of unexpected results, summarized above, we are persuaded that the weight of the evidence on this record sufficiently establishes that the comparable efficacy between the 480 mg/day and 720 mg/day doses would have been unexpected.

c. Petitioner's rebuttal is unpersuasive

Petitioner contends that the results showing that 480 mg/day has efficacy similar to 720 mg/day were not surprising because a person of ordinary skill in the art would have known that the 360 mg/day dose was efficacious. Pet. 53–60; Reply 12–13. To support its position, Petitioner relies on (i) Kappos 2006 and the data in the Kappos 2006 Presentation, (ii) Fox/Gold Article[26] (iii) the EMA Report (Ex. 1037), and (iv) Schimrigk 2004. Additionally, we acknowledge the testimony of Petitioner's experts Drs. Corboy, Benet, and McKeague supporting Petitioner's contention that the efficacy of 480 mg/day DMF was not unexpected. Ex. 1002 ¶¶ 201–215; Ex. 1003 ¶¶ 201–229; Ex. 1004 ¶¶ 24–36.

Petitioner also contends that the DEFINE and CONFIRM trials were designed to compare the efficacy of the 480 mg/day and 720 mg/day doses and, therefore, "[t]o draw efficacy comparisons between 480 mg/day and 720/day would require a non-inferiority study." Pet. 59 (citing Ex. 1002 ¶ 213; Ex. 1004 ¶¶ 31–34).

We consider each of Petitioner's contentions below. For the reasons set forth below, we are not persuaded that Petitioner's rebuttal has overcome Patent Owner's strong evidence of unexpected results.

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[26] Ex. 1036, R. Fox et al., *Dimethyl Fumarate to Treat Multiple Sclerosis*, in MULTIPLE SCLEROSIS THERAPEUTICS 387 (Jeffrey A. Cohen et al. eds., 4th ed. 2011) ("Fox/Gold Article").

i. Kappos 2006, Kappos 2006 Presentation, and Schimrigk 2004

Petitioner first contends that the results of DEFINE and CONFIRM were not surprising because "[s]killed artisans would have immediately recognized from [the Kappos 2006 Presentation] that MS patients who received 360 mg/day DMF during the study had significantly higher disease activity at the start of the study (baseline) than the patients in the other treatment groups." Pet. 54–55 (citing Ex. 1002 ¶¶ 178–180, 203–204; Ex. 1003 ¶¶ 169–172, 207–209).

We incorporate here our findings above regarding the disclosure of Kappos 2006. As above, we determine that a person of ordinary skill in the art would not have found the post hoc calculations of Dr. Benet to be reliable in ascertaining whether the 360 mg/day of DMF was efficacious. Ex. 2060 ¶¶ 42–54; Ex. 2058 ¶¶ 120–126; Ex. 2058 ¶ 130; Ex. 2060 ¶¶ 55–64. That is, while a person of ordinary skill in the art may have been skeptical of the results in Kappos 2006 due to the fact that patients who had been treated with 360 mg/day of DMF had baseline disease activity that was higher than those patients receiving 720 mg/day, we are persuaded, for the reasons discussed above, that the data provided in Kappos 2006 or the Kappos 2006 Presentation would not inform skilled persons on the efficacy of 360 mg/day of DMF in the treatment of MS. Accordingly, we are not persuaded that a person of ordinary skill in the art would have understood Kappos 2006 to teach efficacy in the treatment MS of a 360 mg/day dose of DMF, and determine that Kappos 2006 and the Kappos 2006 Presentation provide little

information suggesting that a dose of 480 mg/day of DMF would have had efficacy in treating MS similar to the 720 mg/day dose of DMF.

Likewise, for the reasons set forth above in Section II.C.1.4, we are not persuaded that a person of ordinary skill in the art would have understood Schimrigk 2004 to teach efficacy in the treatment of MS of a 360 mg/day dose of DMF, and as such, provides little information suggesting that a 480 mg/day dose of DMF would have had efficacy in treating MS similar to the efficacy of a 720 mg/day dose of DMF.

ii. Fox/Gold Article and EMA Report

Petitioner submits the Fox/Gold Article and EMA Report as evidence of what a person of ordinary skill in the art would have known at the time of the invention to rebut Patent Owner's evidence of unexpected results. Pet. 54–59. Both documents were published post-filing and are therefore not available as prior art.

The Fox/Gold Article provides a detailed analysis of data from the phase II study reported by Kappos 2006. Pet. 55–56; Ex. 1036, 6; Ex. 1003 ¶¶ 215–219; Ex. 1004 ¶¶ 24–26. The authors of the Fox/Gold Article acknowledge the discrepancy with baseline Gd+ lesions in the 360 mg/day treatment group noted by Petitioner, and state that the higher mean number of Gd-enhancing lesions at baseline "may have obscured a treatment effect." Ex. 1036, 6.

The EMA Report is a publication by the European Medicines Agency assessing Biogen's application to market Tecfidera® in Europe. Ex. 1037. The EMA reviewed the Kappos 2006 study and acknowledges the discrepancy with baseline Gd+ lesions in the 360 mg/day treatment group

noted by Petitioner and states that "when correcting for the baseline number of Gd-enhancing lesions in the statistical models as a covariate, the effect of the 120 mg TID dosing regimen also reached statistical significance for the various MRI endpoints, at least in one of the requested models." *Id.* at 33–34.

Having considered the Fox/Gold Article, EMA Report, and relevant arguments and evidence, however, we are not persuaded that either the Fox/Gold Article or EMA Report informs us as to what was known at the time of the invention. Rather, we are persuaded by Patent Owner's argument and evidence that each document discloses a post hoc analysis of the data produced by the phase II study reported by Kappos 2006, an analysis performed with the benefit of hindsight and motived by the results of the Phase III DEFINE and CONFIRM studies. PO Resp. 28–31; Ex. 2058 ¶ 140; Ex. 2060 ¶¶ 68–75; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1073 (Fed. Cir. 2012) ("obviousness must be assessed at the time the invention was made"); *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019) ("[A] fact finder must not allow its analysis to be distorted by hindsight bias." (citing *KSR*, 550 U.S. at 421)).

iii. Petitioner's non-inferiority study argument

Petitioner contends that the DEFINE and CONFIRM trials compared 480 mg/day to placebo and 720 mg/day to placebo, which is not the same as comparing 480 mg/day to 720 mg/day. Pet. 59. Petitioner contends that a non-inferiority study, a different type of study, would be required to make any conclusion regarding whether the 480 mg/day dose is equally

efficacious to the 720 mg/day dose. *Id.* (citing Ex. 1002 ¶ 213; Ex. 1004 ¶¶ 31–34); *see* Ex. 1004 ¶ 34 ("My review has identified that the DEFINE and CONFIRM studies were not designed to compare the 480 mg/day dose to the 720 dose—they were simply designed as superiority studies to measure superiority over *placebo only*. . . . Therefore, any conclusion comparing the equivalency of these two doses based on the results of the DEFINE and CONFIRM studies would be improper")).

Patent Owner responds with the argument, supported by evidence, that

> governmental health agencies compared the 480 and 720 mg/day doses without needing a statistical non-inferiority analysis. Ex. 2058 ¶¶ 182–187. The FDA and EMA concluded that 480 and 720 mg/day had "*comparable efficacy*" and statistically significant effects of "*similar direction and magnitude*," respectively. Ex. 2003, 8; Ex. 1037, 75; *see also* Ex. 2004, 48; Ex. 2066, 24–25; Ex. 2060 ¶¶ 104-108; Ex. 1011, 10. This comparison was sufficient for FDA approval of Tecfidera® as a 480 mg/day DMF treatment for MS. Ex. 2003, 8 ("Since the 240 mg tid dose [720 mg/day] offered *no additional efficacy* to the 240 mg bid dose [480 mg/day], I recommend approval of the 240 mg bid dose only."); Ex. 2066, 26.

PO Resp. 54 (emphasis added); *see* Ex. 2066, 24 ("Findings for both the 240 mg bid and 240 mg tid dose groups were highly significant. There was little difference between them.").[27]

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[27] Ex. 2066, FDA, Center for Drug Evaluation and Research, Summary Review (2013) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204063orig1s000sumr.pdf (last accessed April 8, 2019).

Having considered the parties' positions and evidence of record, summarized above, we are not persuaded that a non-inferiority study is required, as Petitioner contends, to reach a conclusion that the 480 mg/day dose is equally efficacious to the 720 mg/day dose. The evidence of record shows that the DEFINE and CONFIRM studies were sufficient for the FDA and EMA to conclude that 480 and 720 mg/day had comparable efficacy such that 480 mg/day was determined to be the "minimum maximally effective dose." Ex. 2066, 26. Accordingly, we are not persuaded that the lack of a non-inferiority study negates Patent Owner's evidence of unexpected results.

d. Conclusion

We evaluate all evidence relating to obviousness, including secondary considerations such as unexpected results, to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d at 1075 (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we are persuaded that Patent Owner's strong evidence of unexpected results of the efficacy of the 480 mg/day dose of DMF outweighs Petitioner's evidence that a person of ordinary skill in the art would have optimized the daily dose of DMF based on the teachings of Kappos 2006 and WO '342. We, thus, conclude that Petitioner has not satisfied its burden of demonstrating, by a preponderance of the evidence, that the subject matter of claims 1–20 of the '514 patent would have been obvious over the combination of Kappos 2006 and WO '342.

F. Ground 4: Asserted Obviousness of Claims 1–20 over the Combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline

For the reasons set forth below, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–20 are unpatentable as obvious over the combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline.

We incorporate here our findings above regarding the disclosure of Kappos 2006.

1. Summary of Additional References Relied Upon

a. Joshi '999 (Ex. 1009)

Joshi '999 relates to the use of dialkyl fumarates, including dimethyl fumarate (Ex. 1009, 6:16–17, 6:60, 8:19), for preparing pharmaceutical preparations for use in transplantation medicine or the therapy of autoimmune diseases, including multiple sclerosis (*id.* at 1:29, 4:45, 8:15), and pharmaceutical preparations in the form of micro-tablets or micro-pellets containing dialkyl fumarates (*id.* at 1:16–20).

According to Joshi '999:

> The dialkyl fumarates used according to the invention may be used alone or as a mixture of several compounds, optionally in combination with the customary carriers and excipients. The amounts to be used are selected in such a manner that the preparations obtained contain the active ingredient in an amount corresponding to 10 to 300 mg of fumaric acid.
>
> Preferred preparations according to the invention contain a total amount of 10 to 300 mg of dimethyl fumarate and/or diethyl fumarate.

Id. at 4:39–48.

b. Clinical Trials

Clinical Trials discloses a proposed study of a "Double-Blind, Placebo-Controlled, Dose-Range Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis." Ex. 1010, 1. The described dose ranges to be tested are essentially the same as the dosages described as having been tested by Kappos 2006. *Id.* at 2. Clinical Trials also states "[a]fter 1 week, Group 3 subjects [who began with 120 mg 3 times/day] who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid." *Id.* Clinical Trials further states "[d]ose reduction will be allowed for subjects who are unable to tolerate investigational drug." *Id.*

c. ICH Guideline

ICH Guideline describes guidelines for determining appropriate dosages of pharmaceutical products. According to ICH Guideline:

> Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs *in individual patients*. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. . . .
>
> Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose response curve for the desired effect), sometimes with adverse consequences (e.g. hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). *This situation has been improved by attempts to*

> *find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses*. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

Ex. 1011, 5 (emphasis added). We understand the "dose-response curve" to represent the relationship of the effect of the drug—beneficial or undesirable—to the dose of the drug. We understand the "plateau of the dose-response curve" to be the portion of the curve in which the increase in the dose does not significantly change the effect of the drug.

Further according to ICH Guideline:

> In adjusting the dose *in an individual patient* after observing the response to an initial dose, what would be most helpful *is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve*. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.
>
> In utilizing dose-response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g. *age, gender, race*), other diseases (e.g. renal or hepatic failure), diet, concurrent therapies, or individual characteristics (e.g. *weight, body habitus*, other drugs, metabolic differences).

Id. at 6 (emphasis added).

"The choice of the size of an individual dose is often intertwined with the frequency of dosing." *Id.* at 7.

ICH Guideline teaches that:

> Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug.

Id.

Following up on discussion on page 7, ICH Guideline further teaches:

> It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.

Id. at 10.

Pages 13 and 14 describe guidance and advice for determining dosages.

2. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline. Pet. 50–53. As in Ground 2, Petitioner relies on Kappos 2006 for its disclosure that 720 mg/day of DMF is an effective MS treatment and for its disclosure that DMF "significantly reduces brain lesion activity, in a dose-dependent manner, as measured by MRI." *Id.* at 51.

Petitioner contends that Joshi '999 discloses treating a patient with MS with a therapeutically effective amount of DMF and notes the existence of gastrointestinal side effects with DMF treatment. *Id.* at 52 (citing Ex. 1009, 5:29–33).

With regard to Clinical Trials, Petitioner contends that

> Clinical Trials describes a two-part study looking at efficacy and safety of 120 mg/day, 360 mg/day, and 720 mg/day of DMF. Clinical Trials states "[a]fter 1 week, Group 3 subjects [who began with 120 mg 3 times/day] who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid." Ex. 1010 at 2. Clinical Trials further states "[d]ose reduction will be allowed for subjects who are unable to tolerate investigational drug." *Id*.

Pet. 52.

Petitioner relies on ICH Guideline for its general guidance in determining appropriate and acceptable drug doses in drug treatments. *Id.*

Petitioner does not expressly set forth its own argument as to why a person of ordinary skill in the art would have had motivation or reason to combine the references relied on by Petitioner. Rather, Petitioner directs our attention to the Final Written decision in IPR2015-01993 and notes that, "[i]n light of these references, the Board found that skilled artisans would have had motivation and a reasonable expectation of success in treating MS patients with 480 mg/day of DMF." Pet. 52.

3. Patent Owner's Contentions

Patent Owner contends that the asserted references do not support Petitioner's position that a person of ordinary skill in the art would have

expected a 360 mg/day dose to be efficacious. PO Resp. 44–45. Specifically, Patent Owner contends that Kappos 2006

> provides no effective dose range nor any motivation or reasonable expectation of success to arrive at the claimed subject matter. Its fundamental deficiencies are not cured by the present four-reference combination.

Id. (internal citations omitted).

Patent Owner further contends that the claims are patentable based on compelling objective evidence. PO Resp. 49–55. In particular, Patent Owner contends that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose, which was appreciated by the FDA and European Medicines Agency. *Id.* (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48; Ex. 2066, 24-25; Ex. 2060 ¶¶ 104–108; Ex. 1011, 10). Patent Owner further contends that Petitioner fails to meaningfully address the Phase III trial results establishing unexpected results. *Id.* at 53–55.

4. Analysis

In this Ground, Petitioner primarily relies on the same teachings of Kappos 2006, as in Grounds 2 and 3. Pet. 50–53. It is undisputed that Kappos 2006 discloses that 720 mg/day of DMF monotherapy is an effective MS treatment and further discloses that DMF significantly reduces brain lesion activity, in a dose-dependent manner. Ex. 1007, 27. As discussed above, however, the evidence of record does not support a finding that any dose other than the 720 mg/day dose of DMF was effective in treating MS. *See, e.g.*, Ex. 2058 ¶ 116 ("Kappos 2006's reference to a 'dose-dependent manner' . . . does not provide any information regarding an effective dose

range but simply identifies only one dose that was effective—720 mg/day of DMF to treat MS.").

Petitioner relies on Joshi '999 for its disclosure of the side effect profile for DMF, relies on Clinical Trials for its disclosure that subjects would be given up to 720 mg/day based on the tolerability of individual patients, and relies on ICH Guideline for its disclosure of general guidance to those developing new drugs or drug treatments in determining appropriate and acceptable drug doses. Pet. 52.

Petitioner relies on ICH Guideline for its disclosure that "drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect)," and that "[t]his situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial." Ex. 1011, 5; Ex. 1002 ¶ 197.

In its Petition, Petitioner fails to articulate its own motivation or reason to combine Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline. Rather, Petitioner relies on the finding of the panel in IPR2015-01993 and notes the following:

> In light of these references, the Board found that skilled artisans would have had motivation and a reasonable expectation of success in treating MS patients with 480 mg/day of DMF. Nevertheless, the Board found the claims not unpatentable based on Patent Owner's unexpected results evidence, and the previous petitioner's complete failure to present any rebuttal evidence on unexpected results. *Id.* at 24, 25 (noting "Petitioner responds [to Patent Owner's unexpected results evidence] with only a single sentence"). As detailed herein, there is nothing unexpected about the magnitude of efficacy of 480 mg/day of DMF in treating MS.

> Independent claims 1, 11, 15, and 20 are therefore obvious over Kappos 2006, Clinical Trials, Joshi '999, and ICH. Ex. 1002 ¶¶ 190-199; Ex. 1003 ¶¶ 190–199.

Pet. 52–53.

We are aware of the panel decision in IPR2015-01993, but do not rely on the outcome of that case here. Rather, we recognize the possibility for a different outcome based on the record developed in this proceeding involving a different party and relying on different evidence. *See Novartis AG, LTS v. Noven Pharms. Inc*., 853 F.3d 1289, 1293–94 (Fed. Cir. 2017) ("It is unsurprising that different records may lead to different findings and conclusions.").

Furthermore, 35 U.S.C. § 312(a)(3), requires that the petition identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim." *See also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) ("In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." (citing 35 U.S.C. § 312(a)(3)). Further, Board rules prohibit incorporating arguments into the petition by reference to other documents. *See* 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Having applied that standard to this Ground, we determine that Petitioner has failed to sufficiently support its obviousness challenge with its own argument and evidence. Consequently, absent a clear articulation of the reasons why the claimed invention would have been obvious, Petitioner's obviousness challenge to claims 1–20 over the combination of Kappos 2006,

Clinical Trials, Joshi '999, and ICH Guideline fails based on the current record.

We note, however, that Petitioner makes one reference in this Ground to the Declarations of Drs. Corboy and Benet to support its contention that "there is nothing unexpected about the magnitude of efficacy of 480 mg/day of DMF in treating MS." Pet. 52–53 (citing Ex. 1002 ¶¶ 190–199; Ex. 1003 ¶¶ 190–199). Even assuming, however, that we were to adopt the previous panel's findings that skilled artisans would have had motivation and a reasonable expectation of success in treating MS patients with 480 mg/day of DMF, which we do not, we are still persuaded on the current record that the claimed subject matter is patentable in view of Patent Owner's evidence of unexpected results. Here, we incorporate our finding discussed above in Section II.E.4 and determine that, on this record, the inventiveness of the claimed subject matter is supported by Patent Owner's strong evidence of unexpected results.

III. CONCLUSION

Having considered all the evidence, Petitioner has not demonstrated by a preponderance of the evidence the unpatentability of claims 1–20 of the '514 patent.

IV. ORDER

Accordingly, it is

ORDERED that claims 1–20 of U.S. Patent No. 8,399,514 B2 are not determined to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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